Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2022**; 27(8): 227
https://doi.org/10.31083/j.fbl2708227

Original Research

Resveratrol-Mediated Gold-Nanoceria Synthesis as Green Nanomedicine for Phytotherapy of Hepatocellular Carcinoma

Adel Ghorani-Azam[1], Javad Mottaghipisheh[2], Mohammad Sadegh Amiri[3], Mohammad Mashreghi[4], Alireza Hashemzadeh[4], Aliakbar Haddad-Mashadrizeh[5], Fahimeh Nourbakhsh[6], Mohabat Nadaf[3], Mohsen Qayoomian[7], Mohammad Ehsan Taghavizadeh Yazdi[7,*], Sara Vitalini[8], Marcello Iriti[9,10,*]

[1]Department of Forensic Medicine and Toxicology, School of Medicine, Urmia University of Medical Sciences, 5714783734 Urmia, Iran
[2]Center for Molecular Biosciences (CMBI), Institute of Pharmacy/Pharmacognosy, University of Innsbruck, 6020 Innsbruck, Austria
[3]Department of Biology, Payame Noor University, 19395-4697 Tehran, Iran
[4]Department of Pharmaceutical Nanotechnology, School of Pharmacy, Mashhad University of Medical Sciences, 13944-91388 Mashhad, Iran
[5]Industrial Biotechnology Research Group, Institute of Biotechnology, Ferdowsi University of Mashhad, 9177948974 Mashhad, Iran
[6]Medical Toxicology Research Centre, Mashhad University of Medical Sciences, 917794-8564 Mashhad, Iran
[7]Applied Biomedical Research Center, Mashhad University of Medical Sciences, 917794-8564 Mashhad, Iran
[8]Department of Food, Environmental and Nutritional Sciences, Università degli Studi di Milano, 20133 Milan, Italy
[9]Department of Biomedical, Surgical and Dental Sciences, Università degli Studi di Milano, 20133 Milan, Italy
[10]National Interuniversity Consortium of Materials Science and Technology (INSTM), 50121 Firenze, Italy
*Correspondence: taghavizadehme971@mums.ac.ir (Mohammad Ehsan Taghavizadeh Yazdi); Marcello.iriti@unimi.it (Marcello Iriti)
Academic Editor: Graham Pawelec
Submitted: 28 April 2022 Revised: 23 May 2022 Accepted: 30 June 2022 Published: 25 July 2022

Abstract

Background: In the present study, resveratrol was used to prepare complexes of cerium and nanoceria, also coated with gold (CeO_2@Au core-shells) to improve the surface interactions in physiological conditions. **Methods**: The CeO_2@Au core-shells were characterized using powder X-ray diffraction (PXRD), Fourier transforms infrared spectroscopy (FTIR), transmission electron microscope (TEM) analysis, dynamic light scattering (DLS) and ζ potential. **Results**: The experiment was led to the successful synthesis of nanosized CeO_2@Au core-shells, although agglomeration of particles caused the distribution of the larger particles. The TEM analysis demonstrated the particles sizes ranged from 20 nm to 170 nm. Moreover, the PXRD analysis showed that both nanoceria and gold with the same crystal systems and space groups. To investigate the anticancer activity of the CeO_2@Au core-shells, the cytotoxicity of the nanoparticles was investigated against liver cancerous cell lines (HepG2). **Conclusions**: The results indicated biosynthesized NCs have significant cellular toxicity properties against HepG2 and could be utilized in hepatocarcinoma therapy. Further *in vivo* investigations is proposed to be designed to assess anti-cancer and safety effects of fabricated nanocomposites.

Keywords: resveratrol; nanogold; cerium oxide; green synthesis; cell toxicity; core-shells; nanocomposite

1. Introduction

Phytoalexins are diverse plant secondary metabolites possessing supportive roles against biotic and abiotic stressors, whereas they have represented potent biological properties [1,2]. Resveratrol (3,4′,5-trihydroxy-trans-stilbene) as a natural polyphenolic phytoalexin, can abundantly found in grapes, peanuts, and berries, while it has recently attracted numerous attentions due to its important biotherapy characteristics [3]. Different investigations have confirmed that resveratrol richness in the stressed leaves [4,5]. Asides from diverse beneficial bioactivity effects of resveratrol, various studies have shown significant cardiovascular protective effects in people who consume rich resveratrol herbal products [6–8]. Resveratrol efficiently targets extracellular ROS when administered orally, consequently acts as a great antioxidant [9]. Furthermore, this compound displays useful effects for the treatment of cancer, hypertensive, inflammatory, Alzheimer' and metabolic diseases [10–13].

The cerium oxide (nanoceria, NCs) have demonstrated anticancer activities, due to its interesting changes in oxidation states, while it can act similar to the antioxidant enzymes (catalase and superoxide dismutase mimetic activities) [14–16], subsequently, showing protective attribute as an active scavenger of reactive oxygen/nitrogen species (ROS/RNS) with unlimited cycles that involves changes in oxidation states of Ce^{3+}/Ce^{4+} [17,18]. The strong anticancer function of the NCs can occur via correcting homeostasis in tumor microenvironment and angiogenesis, preventing myofibroblast formation, invasion and tumor growth without any changes in ROS levels, enhancing the immune system, and in some cases, some paradoxical reports explain the genotoxicity and oxidative stress from ROS formation as the determining factors to death of cancer cells [19–24]. Reports suggest the bioactivity of the NCs are size-, medium-, pH- and time-dependent [25,26].

The combination of NCs with gold could enhance the anticancer effects of the NCs along with the biocompatibility of the particles [27]. Due to the potential application of gold in different nanoplatforms for the treatment of cancer, as an active agent or a nanocarrier, it can be a good choice to form nanocomposites with NCs [28–30]. The gold inertness and its nontoxic nature are of great use in the design of new active nanomaterials and nanocomposites for biomedical applications [31–34]. The factors that can be crucial in determining the final anticancer properties can be the size, shape, and ratio of the components [35,36]. Gold nanoparticles' toxicity is directly proportional to the size of nanoparticles. The larger particles are less toxic, and the smaller ones have substantial toxicity towards cancer cells [37–40]. Therefore, the NC seeds' size influences the bioactivity of CeO_2@Au core-shells. The combination of NCs and gold, and even with other metals would be an innovative approach for advancing new nanomaterials with stronger anti-cancer properties.

Herein, the complexation of a phytochemical resveratrol and Ce^{3+} was occurred because of the oxophilic nature of lanthanide ions. For the first time, the resveratrol and Ce^{3+} complex was used as a precursor to synthesize NCs by thermal treatment. The prepared NCs were coated with gold and the formation of CeO_2@Au core-shells was fully investigated by using the conventional characterization methods. The anticancer properties of CeO_2@Au core-shells and NCs were measured compared with each other to find the effectiveness of the gold core-shells against liver cancer cells.

2. Materials and Methods

2.1 Instruments and Materials

The following analyses were performed for characterization of the nanoparticles: powder X-ray diffraction (PXRD), Fourier transforms infrared spectroscopy (FTIR), transmission electron microscopy (TEM), Dynamic light scattering (DLS), and ζ potential. The materials were purchased from Sigma-Merck merged chemical groups except the stated items.

2.2 Synthesis of CeO_2@Au Core-Shells

To prepare the nanoceria, 0.012 mol resveratrol and 0.004 mol cerium nitrate hexahydrate ($Ce(NO_3)_3.6H_2O$) were dissolved in 100 mL water separately. The resveratrol was sonicated then stirred vigorously. The cerium ion solution was then added dropwise to the first solution under vigorous stirring. After the addition of cerium ion solution, a milky-like appearance of the mixture confirmed the formation of the resveratrol-cerium complex. Then, the complex was separated using centrifugation and put in an oven at 500 °C overnight (8 h). The prepared nanoceria was used without further purifications. Afterwards, 0.5 g of the as-synthesized nanoceria was dispersed in 2.5 mL of a concentrated solution of Chloroauric acid ($HAuCl_4$, 0.2 M). Then, it was centrifuged and washed one time with 10 mL of distilled water (DW) and dispersed again in 10 mL DW. Eventually, a solution of ascorbic acid (100 mL, 1 M) was prepared and dispersed nanoceria was added to this solution dropwise under vigorous stirring. The CeO_2@Au core-shells were separated and washed several times with DW and applied for characterization and biological tests.

2.3 Cell Culture and Toxicity Effect of Biosynthesized NCs

Liver cancer cell line (HepG2) and human foreskin fibroblasts (HFF) were attained from Iran's Pasteur Institute. Cell developmental was performed in RPMI and DMEM media, supplemented with 100 μg/mL penicillin plus 10% FBS, and as a final point transferred to the incubator. In each well of a 96-well plate, cells were seeded, incubated 24 h, and after that the viability of cells was assessed in 24, 48, or 72 h to the biosynthesized NCs at the 0.16, 0.31, 0.63, 1.25, 2.50, 5.00 mg/mL concentrations using MTT assay.

3. Results and Discussion

3.1 Powder X-ray Diffraction (PXRD)

The PXRD confirmed the formation of gold coated nanoceria (CeO_2@Au core-shells), where the peaks of CeO_2 and Au core-shells were compatible with the reference codes of 00-001-0800 and 00-001-1172, respectively (Fig. 1). The crystal systems, space groups and their numbers of both nanoceria and gold core-shells were cubic, Fm-3m and 225. The experimental 2tetha values (d-space, intensity) appeared at 38.48 °(3.34 Å, 42.6%), 44.70 °(2.02, 16.0%), 64.88 °(1.44 Å, 11.9%), and 77.87 °(1.23 Å, 16.3%) were related to the gold layer and the peaks observed at 28.88 °(3.09 Å, 100.0%), 33.39 °(2.68 Å, 36.7%), 47.79 °(1.90 Å, 65.6%), 56.68 °(1.62 Å, 53.3%), 59.42 °(1.56 Å, 8.9%), 69.76 °(1.35 Å, 10.0%), 76.99 °(1.24 Å, 18.3%), and 79.43 °(1.21 Å, 12.0%) were associated with the cerium oxide core.

The calculated 2theta value (d space, intensity, HKL) of cerium oxide were 28.68 °(3.11 Å, 100.0%, 111), 33.28 °(2.69 Å, 25.0%, 200), 47.83 °(1.90 Å, 80.0%, 220), 56.78 °(1.62 Å, 60.0%, 311), 59.60 °(1.55 Å, 10.0%, 222), 69.58 °(1.35 Å, 10.0%, 400), 76.81 °(1.24 Å, 25.0%, 331), and 79.08 (1.21 Å, 16.0%, 420) and the ones for gold layer were 38.27 °(2.35 Å, 42.6%, 111), 44.60 °(2.03 Å, 22.6%, 200), 64.68 °(1.44 Å, 14.1%, 220), and 77.55 °(1.23 Å, 17.0%, 311). The comparison of the calculated and experimental data indicated the successful synthesis of cerium oxide and the reduction of Au^{3+}. According to the Scherrer equation, the crystallite (grain) size was calculated ≈24.2 nm.

3.2 Fourier-Transform Infrared Spectroscopy (FTIR)

The absorption bands of FTIR between ≈3200–3500 cm^{-1} were associated with the hydroxyl groups of the capped ascorbic acid and possibly on the surface of CeO_2 (Fig. 2) [41–43]. The bands at 3100–2840 cm^{-1} can be related to the C–H stretching of ascorbic acid. Ascorbic acid

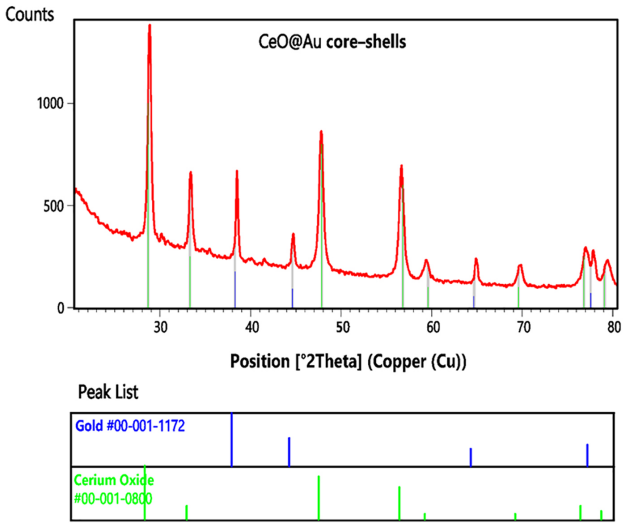

Fig. 1. The PXRD pattern of CeO_2@Au core-shells. The peaks of CeO_2 and Au core-shells were compatible with the reference codes of 00-001-0800 and 00-001-1172.

usually shows at absorption signal at ≈1750–1760, specifically assigned to the carbonyl stretching of the *γ-lactone* ring in the ascorbic acid. The band absence after reduction of gold nanoparticle and bounding to the surface of nanoparticle could prove CeO_2@Au core-shells coated by ascorbic acid [44]. The bands corresponded to C–H bending of the methyl group and carbonate species after calcination was appeared at 1454 and 1385 cm^{-1}, respectively. The bands at 1132 and 1002 were also associated with the C–O stretching of the –OH group of the alcohol. The band observed at 500 cm^{-1} can also be assigned to the Ce–O vibration [45].

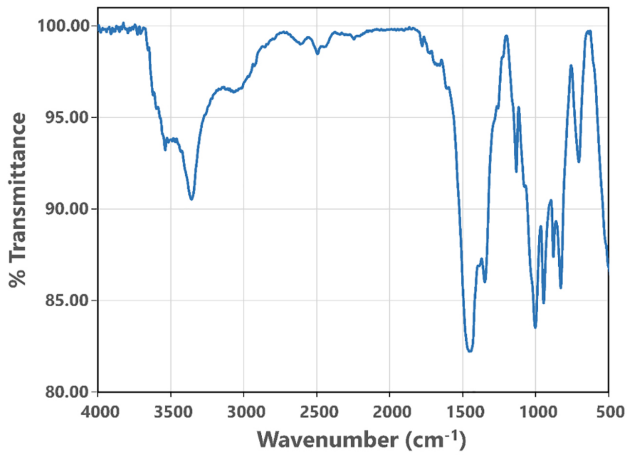

Fig. 2. The FTIR spectrum of CeO_2@Au core-shells. The bands at 1454, 1385, 1132, 1002, and 500 cm^{-1} represents biochemical groups in the formation of NCs.

3.3 Transmission Electron Microscopy (TEM)

The TEM analysis was performed to determine the size of CeO_2@Au core-shells in the solid phase. As shown in Fig. 3, the TEM images have revealed spherical, semi-spherical, and oval morphologies with particles sizes in the range of ≈20–170 nm. The images revealed that the appearance of larger sizes could possibly be due to the agglomeration of the several particles.

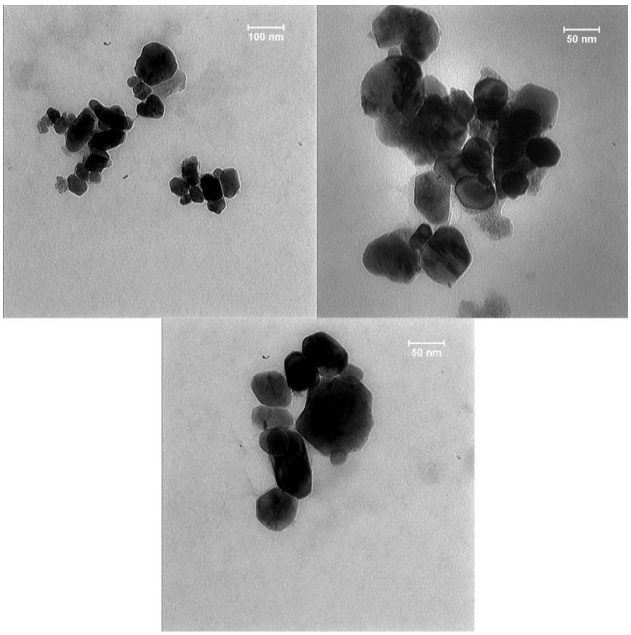

Fig. 3. The TEM images of CeO_2@Au core-shells. The particles sizes are in the range of 20–170 nm.

3.4 Dynamic Light Scattering (DLS) and ζ Potential

The hydrodynamic size and the partial surface charge of the particles were measured using the DLS and ζ potential analyzer (Fig. 4). The analyses revealed the z-average of 229 nm, where nearly 50 and 90% of the particles showed particle sizes under 282 and 468 nm in order, respectively. The particle size according to intensity and number of size dispersion was 262 and 115 nm, respectively, whereas the partial surface charge was –24 mV. The analyses demonstrated that the information obtained from solid-phase sizes and the hydrodynamic sizes were compatible and acceptable. The PXRD and FTIR also confirmed the synthesis of the nanoparticles. The TEM images further indicated an aura around the particles that could be attributed to the formation of a gold layer around the nanoceria particles.

3.5 Anticancer Properties of NC

Nanotechnology-mediated delivery can be employed as a beneficial device in increasing the bioavailability of resveratrol. Nanoscience is an emerging part of investigation that operates at the crossways of biology, physico-

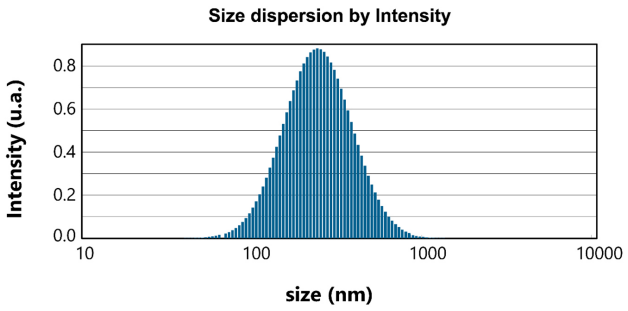

Fig. 4. The hydrodynamic size of CeO_2@Au core-shells.

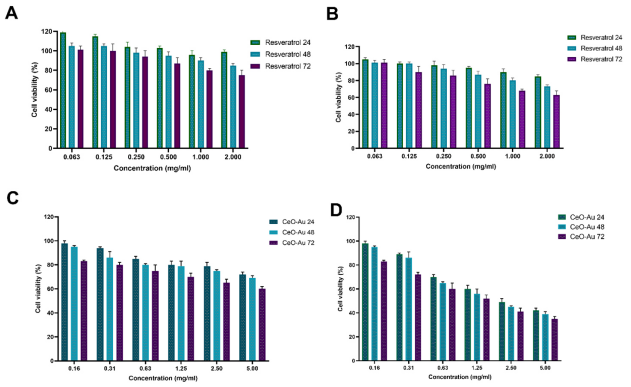

Fig. 5. Cellular toxicity effect of biosynthesized NCs and resveratrol against HepG2 as a cancerous cell lines (B and D) and HFF as a normal cell lines (A and C).

chemicals, engineering, pharmacology, and medicine [22, 46–48]. Designing of NPs (nano particles) for an effective and controlled delivery of anticancer factors is being considered as one of the most important applications of nanoscience [24,49,50]. Few experiments have attempted to study potency of resveratrol for the synthesis of nanoparticles. It has been shown that the solid lipid NPs loaded with resveratrol can cross the cell membrane, while it can be enhanced via increasing the exposure time of cells to resveratrol [51]. Another study utilizing bovine serum albumin-bound resveratrol NPs in primary ovarian cancer of mice showed that not only the NP-bound resveratrol was easier to work with because of the improved solubility, it had also a greater influence on prevent of tumor growth, compared to pure resveratrol [52]. The anti-cancer effect of gold nanoparticles against breast, testicular, liver, and lung cancer cells has been proven in a concentration-dependent manner [30,51–55]. In another study, the produced gold nanoparticles provided a safe and great system for the delivery of gapmers in cancerous cells, which meaningfully down-regulated mutant p53 proteins and changed molecular markers related to cell growth and apoptosis [56].

The anticancer activity of the produced NC was remarkable, whereas it possessed lower toxic effect on normal cells. The results clearly exhibited the toxicity of NC against cancer cells in a concentration and time dependent manner (Fig. 5). Although resveratrol alone was effective against cancer cells, higher efficacy in toxicity against cancer cell lines was observed in combination with nanoparticles.

4. Conclusions

The nanoceria particles were successfully synthesized using resveratrol to form complexes as a precursor for further calcination procedure. The synthesized nanoceria was also coated with a gold layer to increase their anticancer efficiency. The prepared nanoceria were fully characterized and analyzed through conventional methods. The experiment has shown the particle size of ≈20–170 nm in the solid phase with the z-average hydrodynamic size of 229 nm. The present study indicated the successful synthesis of CeO_2@Au core-shells. The anticancer results demonstrated that resveratrol-mediated synthesized NCs have significant cellular toxicity properties against HepG2 and could be utilized in hepatocarcinoma therapy. Further *in vivo* investigations will significantly help to the anticancer and safety effects of fabricated nanocomposites.

Author Contributions

Conceptualization, AGA, JM, FN, METY; methodology, MM, AH, AHM, SV; investigation, AGA, JM, MSA, MM, AH, AHM, FN, MN, MQ, METY, MI; project administration, METY, MI.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors are warmly grateful to the Mashhad University of Medical Sciences for support and kindly providing facilities to perform the experiments.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. MI is serving as one of the Editorial Board and Guest Editor of this journal. We declare that MI had no involvement in the peer review of this article and has no access to information regarding its peer review.Full responsibility for the editorial process for this article was delegated to GP.

References

[1] Jeandet P, Hébrard C, Deville MA, Cordelier S, Dorey S, Aziz A, *et al.* Deciphering the role of phytoalexins in plant-microorganism interactions and human health. Molecules. 2014; 19: 18033–18056.

[2] Modarres M, Taghavizadeh Yazdi ME. Elicitation Improves Phenolic Acid Content and Antioxidant Enzymes Activity in

Salvia leriifolia Cell Cultures. Iranian Journal of Science and Technology, Transactions a: Science. 2021; 45: 849–855.
[3] Zhang L, Li C, Kakar MU, Khan MS, Wu P, Amir RM, *et al*. Resveratrol (RV): a pharmacological review and call for further research. Biomedicine; Pharmacotherapy. 2021; 143: 112164.
[4] Hurtado-Gaitán E, Sellés-Marchart S, Hartwell J, Martínez-Esteso MJ, Bru-Martínez R. Down-Regulation of Phosphoenolpyruvate Carboxylase Kinase in Grapevine Cell Cultures and Leaves Is Linked to Enhanced Resveratrol Biosynthesis. Biomolecules. 2021; 11: 1641.
[5] Souid I, Toumi I, Hermosín-Gutiérrez I, Nasri S, Mliki A, Ghorbel A. The effect of salt stress on resveratrol and piceid accumulation in two Vitis vinifera L. Physiology and Molecular Biology of Plants. 2019; 25: 625–635.
[6] Raj P, Thandapilly SJ, Wigle J, Zieroth S, Netticadan T. A Comprehensive Analysis of the Efficacy of Resveratrol in Atherosclerotic Cardiovascular Disease, Myocardial Infarction and Heart Failure. Molecules. 2021; 26: 6600.
[7] Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. Npj Precision Oncology. 2017; 1: 35.
[8] Dyck GJ, Raj P, Zieroth S, Dyck JR, Ezekowitz JA. The effects of resveratrol in patients with cardiovascular disease and heart failure: a narrative review. International Journal of Molecular Sciences. 2019; 20: 904.
[9] Vestergaard M, Ingmer H. Antibacterial and antifungal properties of resveratrol. International Journal of Antimicrobial Agents. 2019; 53: 716–723.
[10] Ančić D, Oršolić N, Odeh D, Tomašević M, Pepić I, Ramić S. Resveratrol and its nanocrystals: a promising approach for cancer therapy? Toxicology and Applied Pharmacology. 2022; 435: 115851.
[11] Bal NB, Bostanci A, Sadi G, Dönmez MO, Uludag MO, Demirel-Yilmaz E. Resveratrol and regular exercise may attenuate hypertension-induced cardiac dysfunction through modulation of cellular stress responses. Life Sciences. 2022; 296: 120424.
[12] Li M, Li P, Tang R, Lu H. Resveratrol and its derivates improve inflammatory bowel disease by targeting gut microbiota and inflammatory signaling pathways. Food Science and Human Wellness. 2022; 11: 22–31.
[13] Tosatti JAG, Fontes AFDS, Caramelli P, Gomes KB. Effects of Resveratrol Supplementation on the Cognitive Function of Patients with Alzheimer's Disease: a Systematic Review of Randomized Controlled Trials. Drugs Aging. 2022; 39: 285–295.
[14] Dowding JM, Seal S, Self WT. Cerium oxide nanoparticles accelerate the decay of peroxynitrite (ONOO−) Drug Delivery and Translational Research. 2013; 3: 375–379.
[15] Ashna M, Es-Haghi A, Karimi Noghondar M, Al Amara D, Yazdi MET. Greener synthesis of cerium oxide nanoemulsion using pollen grains of Brassica napus and evaluation of its antitumour and cytotoxicity properties. Materials Technology. 2020; 8: 525–532.
[16] Es-haghi A, Javadi F, Yazdi MET, Amiri MS. The Expression of Antioxidant Genes and Cytotoxicity of Biosynthesized Cerium Oxide Nanoparticles Against Hepatic Carcinoma Cell Line. Avicenna Journal of Medical Biochemistry. 2019; 7: 16–20.
[17] Schieber M, Chandel N. ROS Function in Redox Signaling and Oxidative Stress. Current Biology. 2014; 24: R453–R462.
[18] Rahdar A, Beyzaei H, Askari F, Kyzas GZ. Gum-based cerium oxide nanoparticles for antimicrobial assay. Applied Physics A. 2020; 126: 324.
[19] Alili L, Sack M, von Montfort C, Giri S, Das S, Carroll KS, *et al*. Downregulation of Tumor Growth and Invasion by Redox-Active Nanoparticles. Antioxidants Redox Signaling. 2013; 19: 765–778.
[20] Xiao Y-F, Li J-M, Wang S-M, Yong X, Tang B, Jie M-M, *et al.* Cerium oxide nanoparticles inhibit the migration and proliferation of gastric cancer by increasing DHX15 expression. International Journal of Nanomedicine. 2016; 11: 3023.
[21] Sack-Zschauer M, Karaman-Aplak E, Wyrich C, Das S, Schubert T, Meyer H, *et al*. Efficacy of Different Compositions of Cerium Oxide Nanoparticles in Tumor-Stroma Interaction. Journal of Biomedical Nanotechnology. 2017; 13: 1735–1746.
[22] Mousavi-Kouhi SM, Beyk-Khormizi A, Amiri MS, Mashreghi M, Taghavizadeh Yazdi ME. Silver-zinc oxide nanocomposite: from synthesis to antimicrobial and anticancer properties. Ceramics International. 2021; 47: 21490–21497.
[23] Shamasi Z, Es-haghi A, Taghavizadeh Yazdi ME, Amiri MS, Homayouni-Tabrizi M. Role of Rubia tinctorum in the synthesis of zinc oxide nanoparticles and apoptosis induction in breast cancer cell line. Nanomedicine Journal. 2021; 8: 65–72.
[24] Taghavizadeh Yazdi ME, Darroudi M, Amiri MS, Zarrinfar H, Hosseini HA, Mashreghi M, *et al*. Antimycobacterial, Anticancer, Antioxidant and Photocatalytic Activity of Biosynthesized Silver Nanoparticles Using Berberis Integerrima. Iranian Journal of Science and Technology, Transactions a: Science. 2022; 46: 1–11.
[25] Auffan M, Rose J, Orsiere T, De Meo M, Thill A, Zeyons O, *et al.* CeO2 nanoparticles induce DNA damage towards human dermal fibroblasts in vitro. Nanotoxicology. 2009; 3: 161–171.
[26] Li Y, Zhang W, Niu J, Chen Y. Mechanism of Photogenerated Reactive Oxygen Species and Correlation with the Antibacterial Properties of Engineered Metal-Oxide Nanoparticles. ACS Nano. 2012; 6: 5164–5173.
[27] Babu KS, Anandkumar M, Tsai TY, Kao TH, Inbaraj BS, Chen BH. Cytotoxicity and antibacterial activity of gold-supported cerium oxide nanoparticles. International Journal of Nanomedicine. 2014; 9: 5515–5531.
[28] Dash SS, Sen IK, Dash SK. A review on the plant extract mediated green syntheses of gold nanoparticles and its anti-microbial, anti-cancer and catalytic applications. International Nano Letters. 2022; 12: 47–66.
[29] Patil MP, Kim G. Eco-friendly approach for nanoparticles synthesis and mechanism behind antibacterial activity of silver and anticancer activity of gold nanoparticles. Applied Microbiology and Biotechnology. 2017; 101: 79–92.
[30] Mobaraki F, Momeni M, Taghavizadeh Yazdi ME, Meshkat Z, Silanian Toosi M, Hosseini SM. Plant-derived synthesis and characterization of gold nanoparticles: Investigation of its antioxidant and anticancer activity against human testicular embryonic carcinoma stem cells. Process Biochemistry. 2021; 111: 167–177.
[31] Jadhav K, HR R, Deshpande S, Jagwani S, Dhamecha D, Jalalpure S, *et al*. Phytosynthesis of gold nanoparticles: Characterization, biocompatibility, and evaluation of its osteoinductive potential for application in implant dentistry. Materials Science and Engineering: C. 2018; 93: 664–670.
[32] Lim ZJ, Li JJ, Ng C, Yung LL, Bay B. Gold nanoparticles in cancer therapy. Acta Pharmacologica Sinica. 2011; 32: 983–990.
[33] Priya M R K, Iyer PR. Antiproliferative effects on tumor cells of the synthesized gold nanoparticles against Hep2 liver cancer cell line. Egyptian Liver Journal. 2020; 10: 15.
[34] Singh P, Pandit S, Mokkapati V, Garg A, Ravikumar V, Mijakovic I. Gold nanoparticles in diagnostics and therapeutics for human cancer. International Journal of Molecular Sciences. 2018; 19: 1979.
[35] Javad Farhangi M, Es-haghi A, Taghavizadeh Yazdi ME, Rahdar A, Baino F. MOF-Mediated Synthesis of CuO/CeO2 Composite Nanoparticles: Characterization and Estimation of the Cellular Toxicity against Breast Cancer Cell Line (MCF-7). Journal of Functional Biomaterials. 2021; 12: 53.

[36] Mobaraki F, Momeni M, Jahromi M, Kasmaie FM, Barghbani M, Yazdi MET, *et al*. Apoptotic, antioxidant and cytotoxic properties of synthesized AgNPs using green tea against human testicular embryonic cancer stem cells. Process Biochemistry. 2022; 119: 106–118.
[37] AL-Barram LFA. Laser enhancement of cancer cell destruction by photothermal therapy conjugated glutathione (GSH)-coated small-sized gold nanoparticles. Lasers in Medical Science. 2021; 36: 325–337.
[38] Martins P, Rosa D, Fernandes A, Baptista PV. Nanoparticle Drug Delivery Systems: Recent Patents and Applications in Nanomedicine. Recent Patents on Nanomedicine. 2014; 3: 105–118.
[39] Peng J, Liang X. Progress in research on gold nanoparticles in cancer management. Medicine. 2019; 98: e15311.
[40] Yang L, Zhang X, Ye M, Jiang J, Yang R, Fu T, *et al*. Aptamer-conjugated nanomaterials and their applications. Advanced Drug Delivery Reviews. 2011; 63: 1361–1370.
[41] Koleva B, Spiteller M, Kolev T. Polarized spectroscopic elucidation of N-acetyl-l-cysteine, l-cysteine, l-cystine, l-ascorbic acid and a tool for their determination in solid mixtures. Amino Acids. 2010; 38: 295–304.
[42] Hu X, Wei B, Li H, Wu C, Bai Y, Xu X, *et al*. Preparation of the β-cyclodextrin-vitamin C (β-CD-Vc) inclusion complex under high hydrostatic pressure (HHP). Carbohydrate Polymers. 2012; 90: 1193–1196.
[43] Asgharzadeh F, Hashemzadeh A, Rahmani F, Yaghoubi A, Nazari SE, Avan A, *et al*. Cerium oxide nanoparticles acts as a novel therapeutic agent for ulcerative colitis through antioxidative mechanism. Life Sciences. 2021; 278: 119500.
[44] Xiao L, Li J, Brougham DF, Fox EK, Feliu N, Bushmelev A, *et al*. Water-Soluble Superparamagnetic Magnetite Nanoparticles with Biocompatible Coating for Enhanced Magnetic Resonance Imaging. ACS Nano. 2011; 5: 6315–6324.
[45] Farahmandjou M, Zarinkamar M, Firoozabadi T. Synthesis of Cerium Oxide (CeO2) nanoparticles using simple CO-precipitation method. Revista Mexicana de Física. 2016; 62: 496–499.
[46] Es-haghi A, Taghavizadeh Yazdi ME, Sharifalhoseini M, Baghani M, Yousefi E, Rahdar A, *et al.* Application of Response Surface Methodology for Optimizing the Therapeutic Activity of ZnO Nanoparticles Biosynthesized from Aspergillus niger. Biomimetics. 2021; 6: 34.
[47] Mohammadzadeh V, Barani M, Amiri MS, Taghavizadeh Yazdi ME, Hassanisaadi M, Rahdar A, *et al*. Applications of plant-based nanoparticles in nanomedicine: a review. Sustainable Chemistry and Pharmacy. 2022; 25: 100606.
[48] Taghavizadeh Yazdi ME, Nourbakhsh F, Mashreghi M, Mousavi SH. Ultrasound-based synthesis of ZnO·Ag2O3 nanocomposite: characterization and evaluation of its antimicrobial and anticancer properties. Research on Chemical Intermediates. 2021; 47: 1285–1296.
[49] Ghorani-Azam A, Sepahi S, Khodaverdi E, Mohajeri SA. Herbal medicine as a promising therapeutic approach for the management of vascular dementia: a systematic literature review. Phytotherapy Research. 2018; 32: 1720–1728.
[50] Sepahi S, Ghorani-Azam A, Hossieni SM, Mohajeri SA, Khodaverdi E. Pharmacological Effects of Saffron and its Constituents in Ocular Disorders from in vitro Studies to Clinical Trials: a Systematic Review. Current Neuropharmacology. 2021; 19: 392–401.
[51] Teskač K, Kristl J. The evidence for solid lipid nanoparticles mediated cell uptake of resveratrol. International Journal of Pharmaceutics. 2010; 390: 61–69.
[52] Guo L, Peng Y, Yao J, Sui L, Gu A, Wang J. Anticancer Activity and Molecular Mechanism of Resveratrol–Bovine Serum Albumin Nanoparticles on Subcutaneously Implanted Human Primary Ovarian Carcinoma Cells in Nude Mice. Cancer Biotherapy and Radiopharmaceuticals. 2010; 25: 471–477.
[53] Rajeshkumar S. Anticancer activity of eco-friendly gold nanoparticles against lung and liver cancer cells. Journal of Genetic Engineering and Biotechnology. 2016; 14: 195–202.
[54] Shakerimanesh K, Bayat F, Shahrokhi A, Baradaran A, Yousefi E, Mashreghi M, *et al.* Biomimetic synthesis and characterisation of homogenouse gold nanoparticles and estimation of its cytotoxity against breast cancer cell line. Materials Technology. 2022; : 1–8.
[55] Mousavi-Kouhi SM, Beyk-Khormizi A, Mohammadzadeh V, Ashna M, Es-haghi A, Mashreghi M, *et al*. Biological synthesis and characterization of gold nanoparticles using Verbascum speciosum Schrad. and cytotoxicity properties toward HepG2 cancer cell line. Research on Chemical Intermediates. 2022; 48: 167–178.
[56] García-Garrido E, Cordani M, Somoza Á. Modified Gold Nanoparticles to Overcome the Chemoresistance to Gemcitabine in Mutant p53 Cancer Cells. Pharmaceutics. 2021; 13: 2067.